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## **Neuro-oncology in 2013: improving outcome in newly diagnosed malignant glioma**

Weller, M ; Wick, W

**Abstract:** In 2013, two discoveries—that alkylating agent chemotherapy prolongs survival when added to radiotherapy for patients with anaplastic oligodendroglial tumours with 1p19q codeletion, and that bevacizumab prolongs progression-free survival in patients with newly diagnosed glioblastoma—have dominated debate in neuro-oncology. These findings could help to define new standards of care in malignant glioma.

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## Improving outcome in newly diagnosed malignant glioma

Michael Weller<sup>1</sup> and Wolfgang Wick<sup>2</sup>

<sup>1</sup>Department of Neurology and Brain Tumor Center, University Hospital Zurich, and Neuroscience Center, University of Zurich, Zurich, Switzerland; and <sup>2</sup>Department of Neurooncology, Neurology Clinic & National Center for Tumor Diseases, University Hospital Heidelberg, Germany and German Consortium of Translational Cancer Research (DKTK), Clinical Cooperation Unit Neurooncology, German Cancer Research Center, Heidelberg, Germany

**Data from four randomized clinical trials trigger novel research concepts and may define new standards of care in newly diagnosed malignant gliomas: alkylating agent chemotherapy prolongs survival when added to radiotherapy for patients with anaplastic oligodendroglial tumors with *1p/19q* codeletion over radiotherapy alone, and bevacizumab prolongs progression-free survival in patients with newly diagnosed glioblastoma.**

Anaplastic gliomas of World Health Organization (WHO) grade III and glioblastomas (WHO grade IV) are collectively referred to as malignant gliomas. The morphological subclassification of anaplastic gliomas into astrocytic, oligodendroglial or oligoastrocytic (mixed) is challenging and calling for molecular guidance, but has major prognostic significance. In contrast, the morphological subtyping of glioblastoma has no impact on clinical decision making. Maximal safe surgery as feasible followed by radiotherapy of the involved brain region had remained the standard of care for malignant gliomas for decades. The major advances in the

diagnosis and management of malignant gliomas were the stepwise clarification of the prognostic *versus* predictive role of three molecular markers in malignant gliomas, *1p/19q* co-deletion, O<sup>6</sup>-methylguanine DNA methyltransferase (*MGMT*) promoter methylation, and isocitrate dehydrogenase (*IDH*) 1 or 2 mutation, and the introduction of temozolomide (TMZ) chemoradiotherapy for newly diagnosed glioblastoma (TMZ/RT → TMZ).<sup>1</sup> Moreover, recent high-throughput studies have further refined the molecular classification and somatic genomic landscape of glioblastoma.<sup>2,3</sup>

In 2013, long-term follow-up of patients from two randomized clinical trials – European Organisation for Research and Treatment of Cancer (EORTC) 26951 and Radiation Therapy Oncology Group (RTOG) 9402 – demonstrated a major increase in median survival when procarbazine, lomustine (CCNU) and vincristine (PCV) were added to radiotherapy in patients with newly diagnosed anaplastic oligodendroglial tumors with *1p/19q* co-deletions.<sup>4,5</sup> That this difference in outcome between radiotherapy and combined modality treatment was not detected at the first report in 2006 is best explained by the existence of two or more distinct subgroups of patients within the cohort of patients with *1p/19q*-co-deleted tumors. Of note, subgroups of patients with as yet molecularly undefined tumors in the cohort with *1p/19q*-intact tumors seem to benefit from combination therapy, too. Although these observations are largely exploratory and stem from clinical trials insufficiently powered to answer such questions, the similarities in outcome in two independent trials are remarkable and too relevant for patients even prior to prospective validation that they led to changes both in clinical practice and in the current transatlantic clinical trial portfolio: radiotherapy alone should no longer be considered standard of care in patients with *1p/19q*-co-deleted anaplastic oligodendroglial tumors; further, the radiotherapy alone

arm of the CODEL trial (NCT00887146) was replaced by a radiotherapy plus PCV arm. Since PCV is more toxic than temozolomide and since it remains unclear to what extent radiotherapy contributed to the superior outcome in the experimental arms of the EORTC 26951 and RTOG 9402 trials or whether a similar outcome may have been achieved with chemotherapy alone, the revised CODEL trial shall now compare radiotherapy plus PCV *versus* TMZ/RT → TMZ *versus* TMZ alone. Long-term follow-up data from NOA-04, the third relevant anaplastic glioma trial, which compared radiotherapy alone with chemotherapy alone, using TMZ or PCV,<sup>6</sup> may soon indicate whether the hope for improved long-term control by alkylating agent chemotherapy alone is justified and help to validate the predictive biomarker, *1p/19q* co-deletion. While the ongoing trials in anaplastic glioma are increasingly challenging because of demanding logistics and funding required for molecular profiling and long-term follow-up, new insight derived from molecular studies constantly requires reconsideration of our clinical research strategies. Thus, we propose that, at least for clinical trials, the distinction between *IDH-1/2*-mutant and *IDH-1/2*-wildtype tumors should in the future override the distinction between WHO grade II, III and IV tumors and provide guidance for clinical practice as well as trial strategies (Figure).<sup>7</sup>

The major debate in Neuro-Oncology in 2013 focused on the interpretation of outcome and the clinical impact of the AVAGlio and RTOG 0825 trials which explored the efficacy of bevacizumab, a monoclonal antibody targeting vascular endothelial growth factor (VEGF), in the treatment of newly diagnosed glioblastoma.<sup>8,9</sup> Efficacy outcome parameters were similar: progression-free survival was prolonged by 3-4 months whereas overall survival was not improved (Table). Due to differences in the statistical design, the gain in progression-free survival was significant in AVAGlio, but not in RTOG 0825. No particular subgroups defined by age, extent of resection or

*MGMT* promoter methylation status with preferential benefit from bevacizumab were identified. A molecular signature predicting beneficial *versus* detrimental effects of bevacizumab on overall survival as proposed by RTOG requires validation.

Safety and tolerability were overall comparable in both trials and provided no new signals, except contradictory observations on cognitive function and quality of life. AVAGlio reported decreased steroid use and preserved quality of life until progression with bevacizumab whereas RTOG 0825 reported decline in various domains of cognitive function and quality of life in bevacizumab-treated patients prior to progression. Although the test batteries were similar, the time points were not, and testing was enforced by the protocol in AVAGlio more than in RTOG 0825. Central review of neuroimaging in the AVAGlio trial appeared to rule out diffuse, non-enhancing disease progression as a possible explanation for early cognitive decline in bevacizumab-treated patients. While the exploratory analysis of the (albeit) uncontrolled BRAIN trial of single agent bevacizumab in recurrent glioblastoma revealed improvement rather than decline in health-related quality of life and cognitive function,<sup>10</sup> the possibility of adverse interactions between bevacizumab and radiotherapy remains.

Because of the lack of a survival gain and the possibility that some patients may experience adverse effects on cognitive function and quality of life, the use of bevacizumab in newly diagnosed glioblastoma may be attractive particularly in patients with a low chance to benefit from standard radiochemotherapy, i.e., patients with large tumors lacking *MGMT* promoter methylation which also have a low likelihood to receive salvage therapies at progression. This includes a large proportion of the increasing population of elderly patients with glioblastoma. Of note,

these clinically and molecularly defined subgroups of patients have been underrepresented in AVAGlio and more so in RTOG 0825. Meanwhile, controlled trials, like the EORTC 26101 trial (NCT01290939), are required to define the role for bevacizumab in recurrent glioblastoma.

Moreover, biomarkers to predict primary resistance to VEGF inhibition and to identify the biochemical escape pathways from such treatments are urgently needed to better define the place, if any, of VEGF inhibitors in glioma treatment. After three competitor anti-angiogenic agents, enzastaurin, cediranib and cilengitide, have failed in glioblastoma, a final conclusion on whether AVAGlio and RTOG 0825 herald the end or the new beginning of the era of anti-angiogenic therapy for malignant glioma cannot be drawn.

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### Key advances

- 1p/19q testing should be done for all patients with oligodendrogial tumors.<sup>4-6</sup>
- Anaplastic oligodendrogial tumors with 1p/19q co-deletions should no longer be treated with radiotherapy alone, but with alkylating agent chemotherapy, with or without radiotherapy.<sup>4-6</sup>
- The introduction of molecular markers into the next WHO Classification of Tumors of the Nervous System is inevitable.

- Bevacizumab prolongs progression-free, although not overall survival in newly diagnosed glioblastoma.<sup>8,9</sup>
- Current controversies on clinical benefit *versus* safety and toxicity of bevacizumab require further, well-designed prospective clinical trials.

Table

	AVAGlio		RTOG 0825	
	Placebo	Bevacizumab	Placebo	Bevacizumab
	n=463	n=458	n=309	n=311
PFS <sup>1</sup> (months)	6.2	10.6	7.3	10.7
	HR=0.64 (95% CI 0.55-0.74)		HR=0.79 (95% CI 0.66-0.94)	
OS (months)	16.7	16.8	16.1	15.7
	HR=0.88 (95% CI 0.76-1.02)		HR=1.13 (95% CI 0.93-1.37)	

<sup>1</sup>by investigator

Figure. IDH-driven approach to diffuse and malignant gliomas.<sup>1</sup>

<sup>1</sup>Abbreviations: MGMT, O<sup>6</sup>-methyl-guanine DNA methyltransferase; *MGMT*<sup>+</sup>, hypermethylation of the promoter of the *MGMT* gene; *MGMT*<sup>-</sup>, no hypermethylation of the promoter of the *MGMT* gene; PCV, procarbazine, lomustine and vincristine; RT, radiotherapy; TMZ, temozolomide; WHO, World Health Organization



